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Case Report

Antithrombin deficiency with portal vein and superior mesenteric vein thrombosis—a case report

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ABSTRACT

Introduction: A deficiency in antithrombin (AT) can be hereditary or acquired. It is characterized by an AT activity level that is less than 80% of normal or the lower limit of the reference range on a regular basis. In some cases, AT deficiency has been linked to an increased risk of thromboembolism. **Case presentation:** We present the case of a 56-year-old Malay man with long-segment thrombosis of the portal vein and superior mesenteric vein with small bowel ischemia. He was diagnosed with AT deficiency following an extensive hematological and thrombophilia workup supported by a strong familial history of venous thromboembolism (VTE) affecting his brothers and sister. **Conclusion:** Inherited AT deficiency must be considered when spontaneous VTE occurs in young patients with unusual localizations, such as mesenteric veins and portal veins.

Key words: antithrombin deficiency, hypercoagulable, venous thromboembolism

INTRODUCTION

Antithrombin (AT) is a serpin and natural anticoagulant that functions predominantly by inactivating the coagulation factors thrombin and factor Xa and less effectively by inactivating the factors IXa and XIa[1,2] Furthermore, the anticoagulant heparin is dependent on AT for its activity. Heparin binds to AT and increases its anticoagulant activity one thousandfold. AT, like tissue factor (TF) pathway inhibitor, inhibits the TF–factor VIIa complex, preventing factor VIIa from activating factors IX and X[1].

AT deficiency is an autosomal dominant type of thrombophilia affected by serpin family C member 1 (*SERPINC1*) gene mutations[3] and is reported to affect 1 in 500 to 1 in 5,000 people[2,4]. Among Asians, 0.15% of individuals in healthy Japanese populations were estimated to have AT deficiency, which is comparable to the rate in Caucasian populations[5]. Individuals with AT deficiency are more prone to thrombosis. It is expected that 50% of those with congenital AT deficiency will have developed venous thromboembolism (VTE) by the age of 50[6]. Homozygous AT deficiency is uncommon compared to heterozygous AT deficiency, and most homozygosity has been linked to intrauterine death[2].

This case report describes a 56-year-old man with heterozygous AT deficiency who presented with acute abdominal pain due to long-segment thrombosis of the portal vein and superior mesenteric vein and small bowel ischemia.

CASE PRESENTATION

A 56-year-old Malay man presented to the emergency department with a sudden onset of lower abdominal pain that continued for several hours. The pain initially started in the left testicular area and radiated to the left lower quadrant of the abdomen. The pain was extensive and described by the patient as 10/10 on the pain grading scale. The abdominal pain was associated with a fever. He had no other symptoms such as nausea, vomiting, diarrhea, dysuria, or hematuria. He denied any traditional medication or recreational drug use. He used to be a cigarette smoker but had quit for the past 10 years.

The patient had a history of leg swelling 20 years ago but was unsure about the diagnosis. He had no further follow-up and received no further treatment. He had a strong family history of hypercoagulability, as his elder brother had a stroke, and his younger brother and sister had deep vein thrombosis (DVT) and were on anticoagulant treatment. The results of the thrombophilia workups for these patients were not found; they were probably treated at another hospital.

The physical examination revealed that he was afebrile with normal vital signs. The rest of the examination was unremarkable except for generalized lower abdominal tenderness but no guarding or rebound.

The laboratory blood tests reveal the following: a total white cell count of 15.17 $\times$ 10^9/L, a hemoglobin level of 12.7 g/dL, and a platelet count of 413 $\times$ 10^9/L. The

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coagulation test showed normal prothrombin time and activated partial thromboplastin time (12.9 seconds and 36.0 seconds, respectively). He had normal liver and renal function. The autoimmune screening tests, including for antinuclear antibody, complement levels (C3 and C4), rheumatoid factor, and anticardiolipin antibody, were negative.

An ultrasound scan of the patient's abdomen showed free fluid in the subhepatic space, right iliac fossa, and Morrison's pouch. A computed tomography scan of the abdomen performed on a subsequent day showed long-segment thrombosis of the portal vein and superior mesenteric vein with small bowel ischemia (**Figure 1**). He was then treated with subcutaneous fondaparinux for 10 days and showed improvement. He was discharged to his home with a daily oral warfarin dose of 3 mg. He was referred for hemophilia workup during subsequent outpatient follow-up.

A thrombophilia screening was conducted during the subsequent outpatient clinic follow-up (12 months after the thrombotic events) (**Table 1**). The screening revealed that the patient had persistently low levels of AT. Based on his clinical presentation and laboratory findings, he was diagnosed with a heterozygous deficiency of AT. He was then scheduled for life-long anticoagulant therapy for thromboprophylaxis.

He was on 3 mg of warfarin daily with regular international normalized ratio (INR) monitoring. He aimed for an INR between 2 and 3. However, he was having difficulty maintaining the INR within the targeted therapeutic range. He was prescribed rivaroxaban, an orally active direct factor Xa inhibitor. However, rivaroxaban was discontinued after one month due to an inability to tolerate the side effect of epigastric pain. The warfarin was restarted, and currently he is taking a daily 2 mg tablet of warfarin. He was compliant with the treatment, and no other thrombotic or bleeding events have been documented.

DISCUSSION AND CONCLUSION

AT deficiency was discovered in 1965 by Olav Egeberg in a Scandinavian family with VTE. He also determined that the deficiency is an autosomal dominant disorder[7].

AT is a heparin cofactor and a member of the serine protease inhibitor family. The mature AT molecule consists of 432 amino acids and is mainly produced in the liver. AT is a thrombin and factor Xa protease inhibitor. However, AT also has the ability to inhibit factors IXa, XIa, and XIIab; kallikrein; and plasmin[8]. Normal AT plasma levels range from 112–140 μg/mL, with normal AT antigen and activity levels in the range of 80–120%. AT levels are lower in newborns than in adults and somewhat lower in older men and in women who take birth control tablets[4].

Given that AT is one of the major naturally occurring coagulation inhibitors, acquired or inherited deficiencies in this protein result in increased thrombin production[8]. Most of the inherited AT deficiencies are heterozygous. Homozygosity is uncommon and has an increased risk of mortality during pregnancy[7]. In the general population, the incidence has been estimated as 1 in 20 to 1 in 200 people[9]. Meanwhile, 1 in 600 people are born with a congenital AT deficiency[4]. In type I or quantitative deficiency, no abnormal AT is observed in plasma, and the plasma AT ratio of antigen to anticoagulant activity is near 1[10]. Short deletions and insertions are the most common causes of type I AT deficiencies[7].

In type II or qualitative deficiency, a high concentration of AT variants with impaired or null anticoagulant activity is detected in plasma. The risk of thrombosis in patients with type II deficiency is very heterogeneous[10]. Type II AT deficiencies are commonly caused by single base pair substitutions in the reactive domain (type IIa) or in the heparin-binding region of AT (type IIb), resulting in qualitative abnormalities[7]. Mayu *et al.*[11] demonstrated that FS-3Stop and Met32Thr mutations cause type I AT deficiency, whereas Ser116Pro and Ala59Val mutations cause type II AT deficiency, demonstrating the existence of multiple molecular pathways underlying AT deficiency.

Unprovoked DVT, with or without complicated pulmonary embolism, is the most common manifestation observed (approximately 75% of incidents). However, thrombosis may also occur more frequently in atypical venous territories, such as the splanchnic veins (including Budd–Chiari syndrome), vena cava system, and cerebral sinuses[10].

The goal of treatment for patients with inherited AT deficiency is to enhance AT activity (to 120% of normal levels) and maintain AT activity (to 80% of normal levels). Treatment options for those with inherited AT deficiency include plasma-derived AT, heparin, fresh frozen plasma, and human recombinant AT[8]. The first line of care for VTE in patients with AT deficiency is often the same as that for any other patient: (i) consideration of thrombolytics, (ii) initial therapy with heparin or fondaparinux, and (iii) a transition to a vitamin K antagonist. When evaluating individuals with extensive or clinically symptomatic VTE, it may be relevant to consider AT concentration[7].

The most commonly used oral anticoagulants in the treatment of AT deficiency are vitamin K antagonists

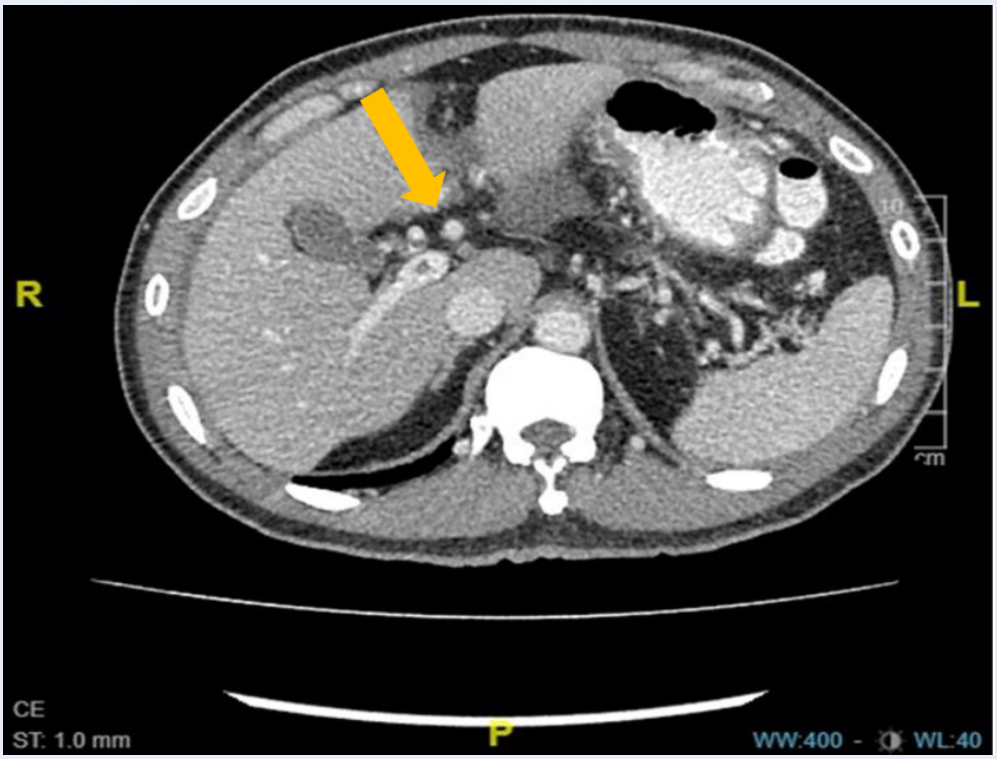

Figure 1: **A computed tomography scan with contrast showed the filling defect of the main portal vein due to thrombosis**.

Table 1: Thrombophilia workup showed persistently low levels of antithrombin activity

Test	Result		Reference range
	July 2017	September 2017	
Protein C activity	125%	128%	70–140%
Free protein S antigen	92%	92%	72–123%
AT activity	46%	52%	83–128%
APCR V Leiden	2.94	3.2	Normal ratio > 2.1

Abbreaviations: **AT**: antithrombin; **APCR**: activated protein C resistance

because they have the most clinical experience and are universally approved in this setting. Direct oral anticoagulants (DOACs), on the other hand, have only recently been offered as a novel and promising therapeutic. DOACs are increasing in popularity, and their use should be considered in patients who have AT deficiency, as these medications work via an AT-independent mechanism [10].

ABBREVIATIONS

AT: Antithrombin, **VTE:** Venous Thromboembolism, **DVT:** Deep Vein Thrombosis, **SERPINC:** Serpin Family C Member 1 (Gene), **TF:** Tissue Factor, **INR:** International Normalized Ratio, **APCR:** Activated Protein C Resistance

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AUTHOR'S CONTRIBUTIONS

Research concept and design: Noor Haslina Mohd Noor, Nur Ilyia Syazwani Saidin, Fatma Basyira Jamallodin; Collection and processing of material: Mohd Nazri Hassan, Abdul Hanan Abdullah; Text writing: Noor Haslina Mohd Noor, Muhamad Aidil Zahidin; Editing: Zefarina Zulkafli; Approval of the

manuscript final version: Salfarina Iberahim, Noor Haslina Mohd Noor. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

This study was carried out in line with the revised Helsinki Declaration. The study was authorised by the institutional review board, and a participant provided informed consent.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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